Hovedoppgave for profesjonsstudiet i psykologi

"Physical exercise did not improve learning in an animal model of Attention-Deficit/ Hyperactivity Disorder."

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Oppgavetittel: “Physical exercise did not improve learning in an animal model of Attention-Deficit/ Hyperactivity Disorder.”

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Abstract

Attention-Deficit/ Hyperactivity Disorder (ADHD) is a neurobehavioral condition characterized by inattentive, hyperactive and impulsive behavior. Over the last years it has been suggested that children with ADHD could benefit from physical exercise close in time before situations that requires concentration and attention, e.g. in school settings. The empirical support for this claim is lacking. The theoretical focus in this paper is on the arousal theories of ADHD, the Dynamic Developmental Theory (DDT) and the Dual-Process theory. The arousal theories explain the behavior seen in children with ADHD as due to an underactivation or underarousal. These theories predict an effect of physical exercise. On the other hand, the DDT and the Dual-Process theory do not predict an effect of physical exercise. The aim of this study was to investigate whether physical exercise has positive effects on behavioral symptoms seen in children with ADHD. This was tested using Spontaneously Hypertensive Rats (SHR), a common and validated animal model in ADHD. The test group had free access to a running wheel in the home cage before tested on an operant conditioning task, the control group did not have this access. The results of the study did not reveal any significant effect of physical exercise. If these data can be generalized to children with ADHD, the practical implications are that behavioral symptoms are not reduced by physical exercise in children with ADHD. The data do not yield support to theories suggesting changed arousal as a causative factor in ADHD. Instead, the data support the effect of reinforcement in the control of behavior.

Innholdsfortegnelse

1 Introduction

Attention- Deficit/ Hyperactivity Disorder (ADHD) is a neurobehavioral condition affecting between 4 % and 12 % of school-aged children today (American Academy of Pediatrics, 2000; Faraone and Biederman, 2005). The most common diagnostic criteria used to diagnose ADHD are the *Diagnostic and Statistical Manual of Mental Disorders, fourth edition* (DSM-IV) (American Psychiatric Association, 2000). According to the DSM- IV, ADHD has to manifest before the age of seven. ADHD is one of the most controversial diagnoses in child psychiatry today (Castellanos and Tannock, 2002) and one of the most studied (Johansen, 2005). Boys are three times more likely to be diagnosed with ADHD than girls (Kessler et al., 2006). Around two thirds of the children with a diagnosis of ADHD also have other comorbid disorders (Stergiakouli and Thapar, 2010).

1.1 Symptoms of ADHD

DSM-IV describes the main clinical symptoms of ADHD as behavioral, and consists of inattention, hyperactivity and impulsivity.

1.1.1 inattention

Attention can be referred to as the relationship between behavior and the environment (Sagvolden, Johansen, Aase, and Russell, 2005). A child with ADHD will, according to DSM- IV, show attention-difficulties in academic performance and/ or social situations and also problems with sustained attention. Sustained attention occurs when a certain stimulus control behavior over time (Sagvolden et al., 2005). The inattentive child is easily distracted and will often show difficulties in completing one task before moving on to the next. The child often fails in given attention to details and has problems with the organization of tasks and activities (DSM-IV). In social setting the inattention may be expressed as frequent shifts in conversations, not listening to what other people say and not be able to follow rules and details in games or activities (DSM-IV).

1.1.2 Hyperactivity

The hyperactive behavior may be manifested by difficulties in sitting still, by running and climbing in inappropriate settings and problems with attending quietly to activities (American Psychiatric Association, 2000). The hyperactive child often fidgets with objects, tap their hands and shake their feet and legs (DSM-IV). Hyperactivity may often vary with the age of the child. Children without a diagnosis of ADHD also show behavior of this kind, but with less frequency and intensity (DSM-IV). The hyperactive behavior is often most salient in children with ADHD and often decreases with age (Taylor and Sonuga-Barke, 2008).

1.1.3 Impulsivity

DSM- IV describes impulsive behavior as impatience, difficulty in delaying responses and problems with awaiting turn. The impulsive child often interrupts other and often fails to listen to directions. The impulsive response is often inaccurate and maladaptive (Solanto et al., 2001). In early childhood the impulsive behavior related to ADHD can be difficult to distinguish from other types of oppositional behavior (Taylor and Sonuga-Barke, 2008). Hyperactive and impulsive behavior tends to decrease with age, but the inattentive behavior is more persistent (Stergiakouli and Thapar, 2010).

Some impairment from these symptoms needs to be present in two or more settings, e.g. at school and at home (DSM-IV). For two- thirds of children diagnosed with ADHD, the symptoms of inattention, hyperactivity and impulsivity will persist adolescence, and also into adulthood (Carr, 2006).

1.2 Subtypes of ADHD

Changes have been made in the diagnostic criteria for ADHD over the past two decades and research has focused on identifying more homogenous subtypes for ADHD (Sagvolden et al., 2005). The DSM-IV now divides ADHD into three subtypes. These subtypes are attention-deficit/ hyperactivity disorder, combined type (ADHD-C), attention-deficit/ hyperactivity disorder, predominantly inattentive type (ADHD-I) and attention- deficit/ hyperactivity disorder- predominantly hyperactive- impulsive type (ADHD-H). The inattentive subtype should be diagnosed if at least six symptoms of inattention (but fewer than six symptoms of hyperactivity and impulsivity) are present (DMS-IV). The inattentive subtype often manifests

as problems in academic settings (Taylor and Sonuga-Barke, 2008). This subtype is harder to identify than the hyperactive- impulsive subtype or the combined subtype. The hyperactive-impulsive subtype of ADHD consists of at least six symptoms of hyperactivity and impulsivity and less than six symptoms of inattention (DSM-IV). The hyperactive- impulsive subtype of ADHD is difficult to identify and distinguish from oppositional disorder (Taylor and Sonuga-Barke, 2008). The combined suptype should been used when at least six symptoms of inattention and at least six symptoms of hyperactivity and impulsivity are present (DSM-IV). The combined subtype is the most common type among children and adolescents with ADHD (Biederman et al., 2002), and will also be the main focus in this paper. According to DSM-IV, the symptoms seen in the three subtypes must be present in the child for at least six months.

1.3 Sex differences

In the literature the inattentive subtype of ADHD is described as more common amongst girls than boys (Biederman et al., 2002; Rucklidge, 2010). Studies show significant sex differences in using Spontaneously Hypertensive Rats (SHR), a validated animal model of ADHD (Berger and Sagvolden, 1998; Bucci, Hopkins, Keene, Sharma and Orr, 2008). A study by Berger and Sagvolden revealed more hyperactive behavior in a group of male SHR than in a group if female SHR, supporting the role of sex differences in the symptoms of ADHD (Berger and Sagvolden, 1998). Bucci and colleagues showed female SHR to be slower in inhibiting a response than male SHR, supporting more cognitive problems in females with ADHD (Bucci et al., 2008). It is important to ask whether ADHD manifests itself differently in boys and girls instead of drawing the conclusion that ADHD is more common amongst boys. A metaanalysis reveal gender differences in the symptoms of ADHD, with girls showing less hyperactive behavior, but more intellectual problems. On the other hand, this metaanalysis did not reveal any gender differences in impulsive behavior. One reason for this could be few available studies for some of the variables (Gaub and Carlson, 1997). The inattentive subtype of ADHD is more often diagnosed in girls (Biederman et al., 2002).

1.4 Treatment

The most common medical treatment for ADHD is methylphenidate (Connor, 2006; Tantillo, Kesick, Hynd and Dishman, 2002). Methylphenidate is a stimulant that affects the dopamine and norepinephrine neurons in the central nervous system (Arnsten, 2001; Connor, 2006). Methylphenidate reduce the symptoms of inattention, impulsiveness and hyperactivity seen in ADHD and shows a positive effect on learning (Connor, 2006; Greenhill, 2001). Methylphenidate is shown to improve working memory (Bedard, Martinussen, Ickowicz and Tannock, 2004). Not all children diagnosed with ADHD benefit from this medical treatment (Hopkins, Sharma, Evans and Bucci, 2009). Taken this into account together with the negative side effects of methylphenidate (Greenhill, 2001), the interest of establishing alternative treatment is increasing. Different behavior therapy methods may also be effective in making the ADHD child more attentive and less active. This can be done in making a task more novel and stimulating or reducing the length of a task (Barkley, 2002)

1.5 A brief history of ADHD

The concept of ADHD has changed from hyperkinetic disorder to minimal brain dysfunction (MBD) to Attention Deficit Disorder (ADD) to ADHD over the years due to changes in the diagnostic manuals. ADHD will be used as the main concept in this paper. ADHD-like behavior was first described in 1902 by George Still. Still linked hyperactive behavior to a lack of moral control in the child, not associated with general intellectual impairments (Still, 2006). In the 1950s, the research on ADHD started to focus on the neurological mechanisms underlying the condition and hyperactive disorders was described as brain damage syndrome (Barkley, 2006) or a minimal brain dysfunction (MBD) (Satterfield and Dawson, 1971). Together with the discovery of the reticular formation came the arousal- and the activation hypothesis of ADHD (Kløve, 1987; Moruzzi and Magoun, 1949; Satterfield and Dawson, 1971; Zentall, 1975). In the late 1980s there was increasing evidence of decreased levels of dopamine in the ADHD brain. Kløve stated in 1987 that it is difficult to understand the functioning of the brain fully without a better understanding of the properties of the brainstem and the thalamic areas. Studies of ADHD have found a genetic component with an estimated heritability of around 76 %, but the exact genes involved are still uncertain. ADHD is thought of as a multifactorial disorder in that many genes, all with small effects, are used in the explanation of the cause of the condition (Faraone et al., 2005; Franke, Neale and Faraone,

2009). Genome-wide association studies (GWAS) has been used in the effort to identify the genetics of ADHD in more detail (Stergiakouli and Thapar, 2010), but no single candidate gene has yet been identified (for more information about the GWAS studies in ADHD, see the metaanalysis by Neale et al., 2010).

The theories of ADHD have developed together with the increased understanding of the brain and the nervous system during the last decades. The exact causes are still not clear (Sonuga-Barke, 2002) and the theories are many. Different explanations for the causes of ADHD are suggested, including underarousal (Zentall, 1975), altered reinforcement mechanisms (Sagvolden, Wultz, Moser, Moser and Mørkrid, 1989; Sagvolden and Archer, 1989), energetic dysfunction (Sergeant, 2000) and behavioral disinhibition (Sonuga-Barke, 2005). Deficits in executive functions are thought to play a role in ADHD, with problems with inhibition as the central behavioral outcome (Barkley, 1997).

Research indicates an inhibitory deficit in children with ADHD (Barkley, 1997), but the explanation behind this deficit varies (Podolski and Nigg, 2001). Using the stop- signal task, Schachar and colleagues found that children with ADHD performed slower than comparison children. They were in fact 70 ms slower to stop an ongoing response, supporting an inhibitory deficit in ADHD (Schachar, Mota, Logan, Tannock and Klim, 2000). The dual-pathway theory of Sonuga-Barke relates ADHD to a deficit in executive functions caused by alteration in the mesocortical dopamine branch in explaining the inhibitory deficit (Sonuga-Barke, 2005). According to the cognitive-energetic model, the inhibitory deficit is caused by a non optimal activation state in the individual (Sergeant, 2005). In the DDT the problems with inhibition of responses seen in children with ADHD is explained as a deficit in the extinction of previously acquired behavior (Johansen and Sagvolden, 2004; Johansen et al., 2009; Sagvolden et al., 2005). The delay aversion could be caused by a motivation to avoid delay as predicted by the dual process theory, or due to a failure to modulate a proper state of arousal as proposed by the cognitive-energetic model.

Children with ADHD perform worse in the slow condition in a go/ no- go task compared to the control children (Börger and van der Meere, 2000). These results support a non-optimal activation state during tasks with relative slow event rates. Another possibility is that the worse performance is due to a lack of motivation because of a delay aversion in the children with ADHD.

This paper will focus on the most common theories of ADHD and those that are relevant for the present study. A brief introduction of each theory will be given, followed by a description of dopamine and physical activity.

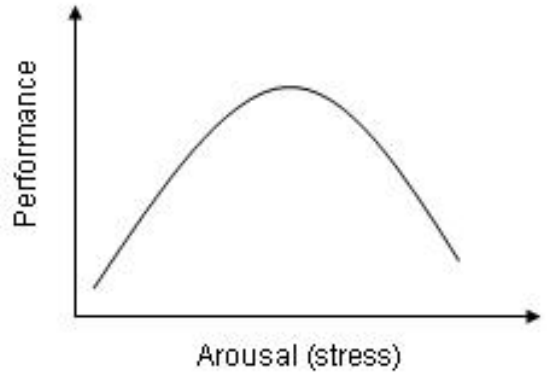
2 Arousal theories of ADHD

The reticular formation was first described by Moruzzi and Magoun in 1949. The reticular formation lies central in the brain stem and consists of neurons of different shape and size. All types of information regarding the senses and signals from higher levels in the brain, like hypothalamus, limbic structures and the cortex, can be integrated by the help of the reticular formation (Brodal, 2007). The reticular formation influences functions localized in the spinal cord, such as muscle tension, breading and blood pressure. The reticular formation also influences activity of the cortex and the level of consciousness (Brodal, 2007; Kløve, 1987). The level of consciousness in the individual varies from intense attention to drowsiness or sleep. Part of the reticular formation is necessary for the maintenance of a normal state of awakefullness (Brodal, 2007). With electric stimulation of the reticular formation in animals under anesthesia, we can see changes in the electrical activity of the cortex as measured by electroencephalography (EEG). These changes can also be observed in humans in the transition from a relaxed condition to a condition of increased vigilance. The activation seen in EEG may be produced by any kind of afferent stimulus that arouses the subject for alertness (Moruzzi and Magoun, 1949). The most important task of the reticular formation is to contribute to the attentional focus of the individual required for processing external stimuli or for internal processes (Brodal, 2007). Arousal or activation refers to the variations in the excitation of the individual. Such excitations can be measures by skin resistance, muscle tension, EEG, cardiovascular measures and other autonomous or cortical measures (Duffy, 1962; Sanders, 1983). Studies have shown changes in the degree of activation in psychiatric disorders (Duffy, 1962).

Based on the behavioral criterion of high levels of motor activity, short attention span, low frustration tolerance and aggressive and impulsive behavior, Satterfield and Dawson described the hyperkinetic syndrome in 1971. They showed that the hyperactive child had higher skin resistance and fewer spontaneous skin resistance responses than control children. Hyperactive children also show a lower degree of EEG arousal compared to non- hyperactive children (Grunewald-Zuberbier, Grunewald and Rasche, 1975). These results supported a physiological underarousal in hyperactive children (Satterfield and Dawson, 1971). A normal person will be awake and conscious of his environment by a certain level of stimulation. When the cortex receives sufficient amount of impulses it is said to be activated or aroused. The cortex is in a state of arousal when a critical number of cortical neurons fires and results

in a proper pattern of activity (Kløve, 1989). Both very high and very low levels of arousal will interfere with functions like attention, concentration, cognition, impulse control and emotional modulation and expression (Kløve, 1989). This can be linked to the inverted-U function first proposed by Yerkes and Dodson in 1908 (Calabrese, 2008). The inverted-U links arousal, performance and stress (Sanders, 1983). At the optimal level of arousal with regard to performance, stress is minimal. When stress increased, arousal and performance will be at a suboptimal level. A high level of stress in the individual will lead to overarousal and poor performance (Sanders, 1983). If we use the inverted-U in explaining ADHD from an underarousal perspective, the child's performance could only be optimal at a medium level of arousal. A too low or a too high level of arousal will decrease the performance. Studies indicate an inverted-U relationship between the dopamine levels in the mesofrontal areas and the efficiency of working memory. Too high or too low levels of dopamine are associated with a decrease in performance (Zahrt, Taylor, Mathew and Arnsten, 1997).

Figure 1: The inverted-U function, first proposed by Yerkes and Dodson in 1908, linking performance with arousal (stress).



2.1 The optimal-stimulation theory

A stimulus reduction theory was first proposed as an explanation of hyperactive behavior by Strauss in the late 1940s. According to this theory, the child's hyperactive behavior was caused by an overstimulation. The hyperactive child was not able to organize incoming stimulation, resulting in disorganized activity. The treatment proposed was a maximal reduction of environmental stimulation, for example no pictures on the walls and the use of the same color on the walls and the furniture (Zentall, 1975). Observations of hyperactive children challenged the stimulus reduction theory. One example, when hyperactive children were isolated from their classmates they tended to create their own stimulation by playing

vigorously and making noise of their own. Zentall described hyperactive behavior as increased activation (Faraone and Biederman, 2005), short attention span, distractibility, impulsiveness, explosiveness, inability to delay gratification and poor performance in school (Zentall, 1975). This description shows a great resemblance to the description of ADHD today. A theoretical alternative to the stimulus reduction theory emerged when one started to look at the hyperactive behavior as possibly valuable for the child. Research started to show that hyperactive behavior actually functioned to optimize stimulation rather than being a consequence of too much stimulation (Zentall, 1975). According to the optimal stimulation theory proposed by Zentall, the high activity level of the hyperactive child might be an attempt to increase an insufficient stimulation rather than a consequence of overstimulation (Zentall, 1975). This give rise to an underarousal in explaining the behavior of ADHD.

2.2 The cognitive-energetic model

The state regulation hypothesis state that a non-optimal energetic state could explain deficit in performance in children with ADHD. The theory suggests that children with ADHD show problems in keeping an optimal state of activation. It requires more effort from a child with ADHD to attain an optimal state of activation (Johnson, Wiersema and Kuntsi, 2009). According to the state-regulation hypothesis, the symptoms of ADHD will increase or decrease depending on the state of the child. The child may become hyperactive during a boring task to increase stimulation (Johnson et al., 2009).

The theoretical fundament for the cognitive- energetic model comes from the model of stress and performance developed by Sanders in 1983 (Sergeant, 2000). In his effort to link arousal, stress and performance, Sanders was the first to create a cognitive-energetic model with the use of Pribram and McGuiness (1975) concepts of effort, arousal and activation (Sanders, 1983). The cognitive- energetic model consist of three levels. The first level contains an encoding stage, a central stage for memory search and a motor stage. These stages are linked to task variables (Sergeant, 2005). The second level of the model consists of the three energetic pools of effort, arousal and activation (Sergeant, 2000). Effort is seen as the coordinator of the arousal and activation systems. Effort is the necessary amount of energy required to meet the demands of a task and to compensate for a sub- optimal energetic state

by modulating the levels of arousal and activation (Sonuga-Barke, Wiersema, van der Meere and Roeyers, 2010). Effort is related to motivation and reinforcement influences this energetic pool (Luman, Oosterlaan and Sergeant, 2005). Factors that affect the effort are variables such as cognitive load (Sergeant, 2000). The effort pool is located in the hippocampus (Sergeant, 2005). The arousal system is seen as a phasic response to input (Pribram and McGuinness, 1975), and is closely related to the reticular formation and amygdala (Sanders, 1983; Sergeant, 2005). Behavioral indications of arousal are indexed by sleep- wake patterns (Sergeant, 2005).The activation system is thought of as a tonic readiness to response (Pribram and McGuinness, 1975), and involves the motor control and coordinating structures in the brain, especially the corpus striatum (Sanders, 1983). Activation is associated with a physiological readiness to respond. The activation pool is affected by different task variables, such as alertness and time of day (Sergeant, 2005). Phasic arousal processes affects the input processes like stimulus encoding, while the tonic activation processes affects the output processes, for example motor preparation (Sanders, 1983) and are associated with the striatum (Sergeant, 2005). The third level of the model is the management or the executive function system. This level is associated with planning of behavior, monitoring, detection of errors and problem solving. The ability to inhibit responses is located in this level (Sergeant, 2000). The executive function is located in the prefrontal cortex (Sergeant, 2005).

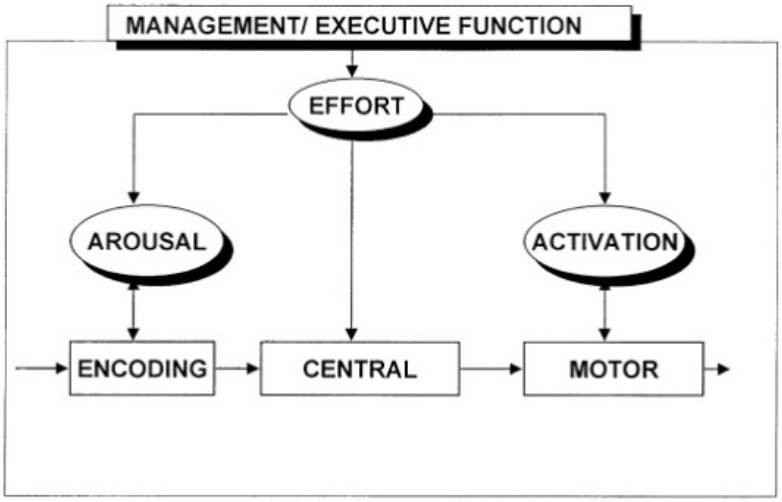


Figure 2: The cognitive- energetic model (Sergeant et al., 2002). The model consist of three levels; a lower level of an encoding stage, a central stage for memory search and a motor stage, a middle level of the three energetic stage of arousal, effort and activation and an upper level of executive function.

The ability to inhibit a response is dependent on the energetic state of the child. According to the cognitive- energetic model, ADHD is caused by an inhibitory deficit resulting in a failure to delay responding (Sergeant, 2000). This deficit in the ability to inhibit a response is due to an energetic dysfunction in the ADHD child (Sergeant, 2005). Disinhibition is best operationalized as a failure to suppress inappropriate responding in a so called go/ no-go task (Sergeant, 2000). In a go/no- go task the child is instructed to make a response to one stimuli and to not make a response to another stimuli, e.g. to different visual signs on a screen (Podolski and Nigg, 2001). The speed in which a stimulus is presented is called an event rate. An individual's energetic state depends on the event rate. A fast event rate will produce an overarousal and a slow event rate will produce a state of underarousal in the individual. Studies supporting the cognitive- energetic model have found that ADHD children perform more poorly in conditions of relative slow event rates compared to fast and moderate event rates (Sergeant, 2000; Wiersema, van der Meere, Roeyers, Van and Baeyens, 2006) due to an inability to produce the necessary amount of effort (Johnson et al., 2009). Deficits in performance seen in ADHD children may reflect a mismatch between the actual state the child is in and an optimal state required to perform a particular task (Sergeant, Oosterlaan and van der Meere, 1999). The ADHD child is unable to modulate their physiological state to meet the demands of the actual tasks and settings (Sergeant, 2000). The problem with state regulation seen in children with ADHD is due to underactivation. According to the cognitive energetic model, the ADHD child suffers from a deficit in the energetic pool of effort. This

will lead to an underactivation in the child, resulting in poor performance. Reinforcement control the effort pool, so reinforcement will produce the necessary amount of energy required to fulfill a task (Luman et al., 2005). In this sense the cognitive energetic model also includes motivation and reinforcement in explaining the behavior of ADHD.

3 Dopamine

The most interesting neurotransmitter concerning ADHD is dopamine (Nieoullon, 2002; Sagvolden and Sergeant, 1998; Sagvolden, Russell, Aase, Johansen and Farshbaf, 2005). Dopamine is, together with norepinephrine, epinephrine and serotonin, monoamines that modulate signal conduction in the central nervous system. Catecholamines are a subclass of monoamines, consisting of dopamine, norepinephrine and epinephrine. Monoaminergic neurons modulate the function of many different regions in the brain and serve to increase or decrease activity of particular brain functions (Carlson, 2007). Dopamine is involved in regulation of brain output and behavior (Nieoullon, 2002) and plays an important role in movement, attention, learning and reinforcement (Carlson, 2007; Schultz, 2002). The three most important dopamine systems originate in the substantia nigra and in the ventral tegmental area, both located in the midbrain. The nigrostriatal system originates in the substantia nigra and projects to the neostriatum. The neostriatum is involved in the control of movement. The mesolimbic system and the mesocortical systems are both originating in the ventral tegmental area. The mesolimbic system projects to parts of the limbic system, including nucleus accumbens, amygdala and hippocampus. The nucleus accumbens plays a central role in the reinforcement of behavior. The mesocortical system projects to the prefrontal cortex, affecting functions such as short- term memory, planning and problem solving (Carlson, 2007).

About 75 % of the dopamine neurons shows a phasic activation when animals are faced with a reinforcer, like food or water (Schultz, 2002). This dopamine activation seems to occur when the link between a reinforcer and a response is not well established, for example when novel stimuli are presented (Sagvolden et al., 2005; Schultz, 1998). When an unpredicted reinforcer is presented, the dopamine activation will increase. When a predicted reinforcer is not delivered, the dopamine activation will decrease, starting an extinction process of the learned behavior (Schultz, 2002). This give rise to the important role of dopamine in learning processes (Sagvolden et al., 2005; Schultz, 1998).

3.1 The role of dopamine in ADHD

There is now a general agreement that a dysfunction in the dopamine system is central in explaining ADHD (Krause, K., H., Dresel, Krause J., la Fougere and Ackenheil, 2003; Nieoullon, 2002; Sagvolden and Sergeant, 1998; Sagvolden et al., 2005), although the exact genetic architecture is rather complex (Faraone et al., 2005). The positive responses to stimulant medication such as methylphenidate support the role of dopamine in the etiology of ADHD (Beninger, 1989). It is difficult to select just one gene involved in the explanation of ADHD and studies give rise to the thought that ADHD is mediated by many different genes, each with a small effect (Faraone et al., 2005). It is possible that hyperactive behavior and poor impulse control seen in ADHD is due to too much activity in the striatum and/or the nucleus accumbens (Solanto, 2002).

The documented role of dopamine in reinforcement of behavior gives rise to the role of dopamine in explaining ADHD. As we shall see later in this paper, both the dynamic developmental theory and the dual-pathway model of ADHD support the role of dopamine in the etiology of ADHD by introducing concepts like reinforcement (Sagvolden et al., 2005) and delay aversion (Sonuga-Barke, 2003).

4 The dynamic developmental theory

The dynamic developmental theory (DDT) of ADHD is primarily a behavioral theory inspired by behavioral analysis. The theory is also based on neurobiological factors, primary the interaction between dysregulated fronto-striatal circuits and hypofunctioning dopamine system (Sagvolden et al., 2005). According to the DDT, the two main behavioral processes causing ADHD is reduced reinforcement of novel behavior and deficient extinction of previously reinforced behavior (Sagvolden et al., 2005). These two processes will lead to changes in basic learning mechanisms (Johansen, 2005; Sagvolden et al., 2005). The resulting ADHD behavior is mainly caused by a dysfunctioning meso- limbo- cortical dopamine branch (Johansen, Aase, Meyer and Sagvolden, 2002).

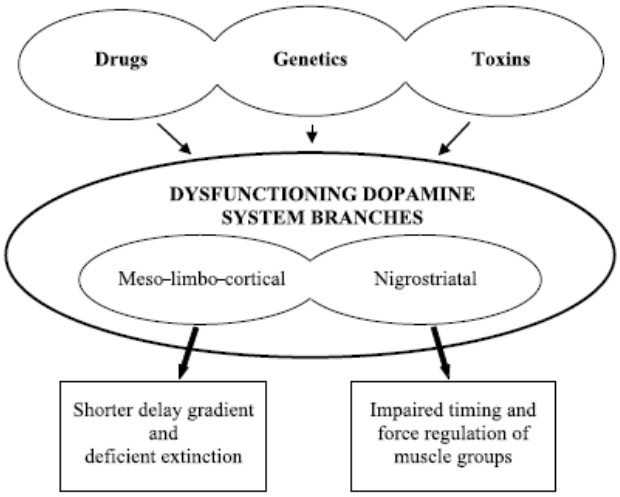


Figure 3: According to the DDT, ADHD behavior is caused by dysfunctioning dopamine branches (Johansen et al., 2002).

4.1 Reinforcement and extinction

Reinforcement and extinction are both behaviorally defined concepts associated with dopamine neuron activity (Sagvolden et al., 2005). A reinforcer acts as a guide to behavior (Johansen et al., 2009) and is needed both in acquisition and in maintenance of behavior. Reinforcement of behavior gives rise to new learning (Beninger, 1989). The effect of a reinforcer depends on the individual's ability to keep preceding behavior and stimuli in the situation active in mind. In this sense, the reinforcer works as a guide to behavior (Johansen et al., 2002). A reinforcer will enhance the likelihood that the reinforced behavior will be

repeated later in the same or in a similar situation (Sagvolden et al., 2005). Studies have shown that altered reinforcement processes are important in the symptomathology of ADHD (Johansen, Sagvolden and Kvande, 2005). The effect of a reinforcer is largest when it's given immediately after a response and wanes as a function of time (Johansen et al., 2002). Longer time interval between response and reinforcer, will reduce the effect of the reinforcer (Sagvolden et al., 2005). On a behavioral level, extinction is also defined in relation to reinforcement (Johansen et al., 2009; Sagvolden et al., 2005). Responding will be maintained as long as reinforcers are delivered (Sagvolden et al., 2005). When reinforcers are no longer delivered, an extinction process starts (Johansen et al., 2002). A child with ADHD is to a lesser degree able to stop a behavior that is no longer reinforced than other children. The slower extinction process are shown in studies using animal models of ADHD and in studies with children (Aase and Sagvolden, 2006; Johansen and Sagvolden, 2004). At a behavioral level, extinction will produce an increased number of responses and an increased behavioral variability (Sagvolden et al., 2005). As mentioned earlier, reinforcement and extinction is rather different at a neurobiological level. Reinforcement is associated with a phasic activation of dopamine neurons and extinction is related to depression of dopamine activation (Schultz, 2002).

4.2 The delay-of-reinforcement gradient

The relationship between the effect of the reinforcer and the time interval between response and reinforcer is known as the delay-of-reinforcement gradient (Catania, Sagvolden and Keller, 1988; Sagvolden et al., 2005).

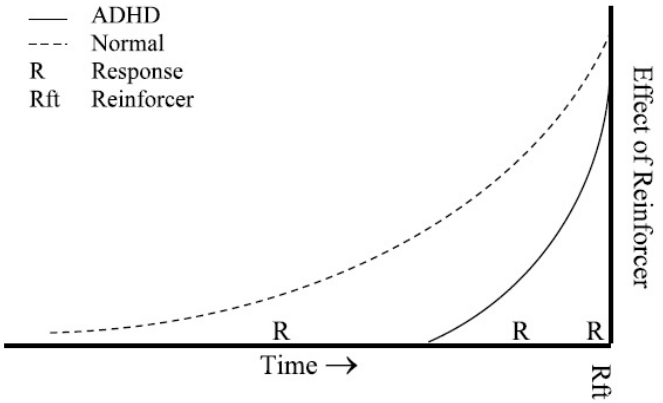


Figure 4: The delay-of-reinforcement gradient (Johansen et al., 2002). This gradient is shorter and steeper in ADHD children than in normal children, resulting in a narrower time window for an association between a response and a reinforcer to take place (Sagvolden et al., 2005).

According to the DDT, a shorter and steeper delay- of- reinforcement gradient explains the ADHD symptoms (Sagvolden et al., 2005). The shorter and steeper delay-of-reinforcement gradient may be a result of a dopaminergic dysfunction (Johansen et al., 2009). Mainly the reinforcers that are given close in time to the behavior will be effective (Johansen et al., 2002), because the ADHD child is not able to link the behavior and the reinforcer if the time interval between the behavior and reinforcer is long. On a behavioral level this will produce poor sustained attention, hyperactivity and impulsivity, which in turn affects learning processes (Sagvolden et al., 2005). Inter response times (IRTs) is the relations between responses. Due to the shorter delay gradient seen in children with ADHD, only responses with short IRTs will be reinforced (Sagvolden et al., 2005).

5 The dual-pathway model of ADHD

The executive dysfunction theory and the delay aversion theory has for a long time been looked at as two separate theories of ADHD. The heterogeneity of ADHD raises the possibility for more than one explanation of the disorder (Sonuga-Barke, 2003). Sonuga-Barke argues for two possible pathways to explain ADHD.

5.1 The executive dysfunction theory

The first pathway explains ADHD as a disorder of dysregulation of thoughts and action associated with poor inhibitory control. As mentioned earlier, response inhibition is the ability to inhibit an ongoing response (Barkley, 1997; Sonuga-Barke, 2005).The poor inhibitory control leads to lack of control strategies in the ADHD child, resulting in impulsive behavior (Schachar, Mota, Logan, Tannock and Kim, 2000). The problem with response inhibition is seen as a cognitive pathway associated with executive dysfunction (Dalen, Sonuga-Barke, Hall and Remington, 2004). Executive functions represent "top- down" cognitive input that facilitate decision making by maintaining information in working memory and integrate this knowledge with information about the current context to identify the optimal action for the given situation (Willcutt, Doyle, Nigg, Faraone and Pennington, 2005). Executive functions are defined as neurobiological processes that maintain an appropriate problem solving set to attain a future goal. A stop signal task has been used to investigate the response inhibition deficit seen in children with ADHD. During a stop- signal task, the child has to inhibit a response to a primary task when a stop signal is presented (Oosterlaan, Logan and Sergeant, 1998). A meta-analysis of the stop- signal task supported poor response inhibition in children with ADHD (Oosterlaan et al., 1998).

5.2 The delay aversion theory

According to the other pathway in the dual pathway model, ADHD is caused by a delay aversion associated with alterations in reward mechanisms (Sonuga-Barke, 2002). According to the delay aversion pathway, a biologically-based shorter delay reward gradient leads to a tendency in the child to prefer a reward immediately (Sonuga-Barke, 2003). The delay aversion hypothesis states that the ADHD behavior is caused by an underlying motivational style. The hypothesis is seen as an alternative to the cognitive theories of ADHD (Sonuga-

Barke, 2005). The child with ADHD is motivated to avoid or escape delay, which results in inattentive, impulsive and hyperactive behavior (Sonuga-Barke, 2002). When the ADHD child is given a choice between an immediately reward and a later reward, the choice will fall on the immediately reward even in cases when the later reward is bigger (Sonuga-Barke, 2003; Tripp and Alsop, 2001).

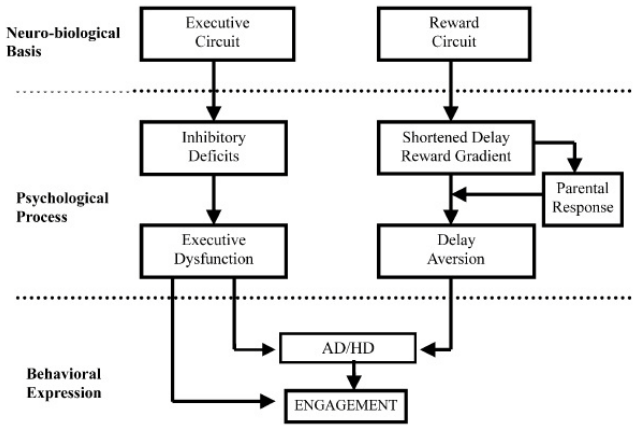


Figure 5: The dual pathway model of ADHD. The left pathway represent ADHD as an inhibitory deficit associated with executive dysfunction. The right pathways represent ADHD as a delay aversion (Sonuga-Barke, 2003)

5.3 Integrating the two theories

The executive pathway is associated with a cognitive deficit and the delay aversion pathway is associated with an altered motivational style. In this sense, the two pathways are rather distinct (Sonuga-Barke, 2003). The two pathways are linked together on a neuro biological level, in that they are both associated with dysfunctions in dopamine branches (Sonuga-Barke, 2003). The dual-pathway model indicates that inhibitory deficits are a result of alterations in the executive circuit modulated by the meso-cortical dopamine branch and the nigro-striatal dopamine branch. Delay aversion is, according to the model, caused by alterations in the meso-limbic dopamine branch (Sonuga-Barke, 2005). The dual-pathway model gives a better explanation of the heterogeneity behind the condition, especially the combined sub-type. The combined sub-type of ADHD is the common clinical outcome of problems with response

inhibition and delay aversion, together producing impulsive, inattentive and hyperactive behavior (Sonuga-Barke, 2003). Research has supported the role of response inhibition and delay aversion in the explanation of ADHD (Solanto et al., 2001).

6 Physical activity

It is widely accepted that physical exercise has a positive effect on our body. Moderate amount of exercise reduce the risk of obesity, cardiovascular diseases, type 2 diabetes, osteoporosis and cancer (Dishman et al., 2006). Physical exercise has also been studied extensively because of its potential effect on mental health (Hopkins et al., 2009). Studies supports that behavioral stimulation and exercise can help us maintaining and improve good brain health and plasticity throughout life (Cotman and Berchtold, 2002; Dishman et al., 2006; Meeusen, 2005). There is increasing evidence that exercise can be helpful in reducing depressive symptoms both in the healthy and the clinical populations and improves cognitive functioning (Hopkins et al., 2009; Meeusen, 2005; Pietropaolo et al., 2008; Vaynman, Ying and Gomez-Pinilla, 2004). Physical exercise is shown to influence the central dopaminergic, serotonergic and noradrenergic systems in the brain by alter transmission in these systems (de Castro and Duncan, 1985; Hattori, Naoi and Nishino, 1994; Meeusen and De, 1995; Winter et al., 2007). A study performed by Winter and colleges in 2007 showed an improvement in learning immediately after intense physical exercise. The individuals that ran two sprints of less than three minutes learned 20 percent faster compared to moderate exercise or being sedentary. The study also revealed increased dopamine levels after physical exercise (Winter, 2007). McMorris and colleagues did not revealed any effect of exercise on performance. Instead of an arousal theory in explaining individual performance, their focus is on the cognitive abilities of the individual. With the necessary cognitive abilities, the individual can perform well on e.g. a decision making task independent of a high or low arousal level (McMorris et al., 1999).

6.1 Physical activity and ADHD

In view of the support for the general benefits of exercise in different normal and clinical populations, a relevant question raised today is whether physical exercise also can have an effect on the symptoms seen in ADHD. Reports from parents and teachers have proposed that ADHD children can benefit from physical exercise (Tantillo et al., 2002). Few studies have examined the effects of exercise on humans with ADHD, and the results of those that exist are mixed (Tantillo et al., 2002). Tantillo and colleagues argues for methodological problems in four known studies on the effects of physical activity on children with ADHD. In a study

from 2002, Tantillo and colleagues used spontaneous eye blink and the acoustic startle eye blink response (ASER) to test the effect of exercise on ADHD children. ASER measures the dopaminergic activity in the brain. The finding of Tantillo and colleagues supports an effect on ADHD behavior after exercise (Tantillo et al., 2002).

Although the studies on the effect of physical exercise on the symptoms of ADHD are few, the increase in dopamine levels due to physical exercise is more established. A study with Wistar/ST rats demonstrated increased dopamine levels in the striatum after treadmill running (Hattori et al., 1994). These findings are supported by a study of Petzinger and colleagues. After treadmill exercise, the striatal dopamine levels in the brain of mice increased. This study showed altered dopaminergic activity, giving rise to the importance of physical exercise in maintaining optimal dopamine levels (Petzinger et al., 2007).

6.2 Do the models predict an effect of physical activity?

In the optimal stimulation theory, the behavior seen in ADHD is caused by an underarousal. Activity is considered to be a regulator which maintains an optimal stimulation in the child. According to the optimal stimulation theory, one can predict that a higher level of activity will enhance individual performance, giving rise to an effect of physical activity on the behavioral symptoms of ADHD. The cognitive-energetic model also obviously predicts that physical exercise will increase the state of activation in the ADHD child to a more normal level and thereby improve performance. On the other hand, the DDT says nothing about an effect of physical exercise on the behavioral symptoms of ADHD. Due to a shorter and steeper delay-of-reinforcement gradient, the time window for linking a response to a reinforcer is narrower in the ADHD child. The shorter and steeper gradient is caused by a dopamine hypo functioning (Sagvolden et al., 2005). A certain amount of dopamine release is necessary for an association between a response and a reinforcer to take place (Johansen et al., 2009). Enhanced activity raises the level of dopamine in the brain (de Castro and Duncan, 1985). There is a possibility that this can link physical activity to a better performance, but this is not implied in the DDT today. The dual-pathway model explains ADHD from two different pathways. The first pathway is associated with an executive dysfunction, producing a response disinhibition. The other pathway is associated with a different motivational style,

producing delay aversion. Looking at the dual-pathway model of ADHD, there are no indications to predict an effect of physical activity.

7 The animal model

The rodent model used in the presenting study is the spontaneously hypertensive rat (SHR). The SHR strain is bred from the Wistar Kyoto Rats (WKY) (Okamoto and Aoki, 1963). SHR is a common and validated animal model of ADHD (Hopkins et al., 2009; Sagvolden et al., 2009). There are several advantages of using animal models in research, including a simpler nervous system, more controllable environmental factors and often a more homogenous group genetically speaking (Sagvolden, 2000; Sagvolden et al., 2009). For an animal model to be a good model of a condition or a disorder, certain validation criteria need to be fulfilled (Sagvolden, 2000). Face validity, construct validity and predictive validity are central for an animal model to be valid (Sagvolden et al., 2005; Sagvolden et al., 2009). Face validity is the model´s ability to mimic the behavioral characteristics of a disorder, representing the empirical status of a model. For a model to fulfill the criteria of construct validity, it needs to represent the theoretical rationale for the disorder. Predictive validity is the model´s ability to predict previously unknown aspects of the disorder, like behavior, genetics and neurobiology. Both construct validity and predictive validity are the theoretical status of a model (Sagvolden et al., 2005). For an animal model to fulfill the criteria of face validity, impulsiveness should develop gradually over time, deficit in sustained attention should only be demonstrated when stimuli is widely separated in time and hyperactivity should not be shown in novel situations (Sagvolden et al., 2005). The agreement of the theoretical rationale for ADHD is still limited. This makes it difficult to conclude on the construct validity of the disorder. For the criteria of predictive validity to be fulfilled, the model needs to provide some new useful information (Sagvolden et al., 2005).

SHR shares many of the characteristics of ADHD, including the behavioral symptoms of inattention, hyperactivity and impulsivity and altered dopaminergic and noradrenergic genetics (Sagvolden et al., 2009; Sagvolden et al., 2005). Sex differences have also been observed in the SHR, in that the male show a more hyperactive behavior than the female (Berger and Sagvolden, 1998).

The effects of physical training in rodents have usually been tested by the use of running wheels or treadmills, either by forced running in daily or weekly sessions or by free access to a running wheel (Pietropaolo et al., 2008). An advantage with the use of voluntary running is

that the animals can choose how much to run. This free choice will reduce the amount of stress in the animal (Cotman and Berchtold, 2002).

A study by Hopkins and colleges in 2009 examined the effect of physical exercise on attention and social behavior in two groups of SHR, with and without access to a running wheel. The results showed that exercise had a positive effect on attentional responses in the female SHR, but not in the male SHR (Hopkins et al., 2009). Another study performed by Hoffmann, Elam, Thorén and Hjorth in 1994 showed that voluntary running in a group of SHR affected the monoamine level in specific regions of the central nervous system (Hoffmann, Elam, Thorén and Hjorth, 1994).

8 The problem

As mentioned above, many parents and school teachers today suggest that children with ADHD will benefit from physical exercise (Tantillo et al., 2002). It is however, difficult to find scientific support for this claim. The aim of the presenting study is to investigate whether physical activity will reduce the behavioral symptoms of ADHD. The main question for this study is whether SHR behavior will normalize when the rat has free access to a running wheel, inducing a lot of activity, compared to SHRs without access to a running wheel. According to the arousal theories, we predict that physical exercise will lead to a better performance in the individual. The DDT and the Dual-process theory, however, predict no improvement after physical exercise.

9 Methods

9.1 Subjects

Since the substrain from Charles River, Germany: NCrl is the validated rodent model of ADHD Combined subtype (Sagvolden et al., 2009), only SHR/NCrl rats were used in this study. No other substrain was used as controls, because we were interested in investigating effects of physical exercise on ADHD-combined like behavior. 32 rats were randomly divided into four groups. Group 1 consisted of eight SHR male controls, group 2 of eight SHR male exercises, group 3 of eight SHR female controls and group 4 of eight SHR female exercises. One animal in the female exercise group was later removed from the study.

All the rats were kept at the University of Oslo. The rats were housed individually in 41 x 25 x 25 (height) cm transparent cages. The rats had free access to food (RM3 (E) from Special Diet Services, Witham, Essex CM8 3AD, UK) and free access to water at all times before the habituation session. Before the habituation session, the rats were deprived of water for 12 hours a day. According to Sagvolden and Xu (2008), this is considered a moderate, but sufficient deprivation for motivating the animal.

The study was approved by the Norwegian Animal Research Authority (NARA), and was conducted in accordance with the laws and regulations controlling experiments/ procedures in Norway.

9.2 Apparatus

Running wheels of the type Trixie from Oslo Zoo Senter were used in the study. These are metal wheels with a diameter of 23 cm.

Figure 6: The running wheel used in the presenting study. The picture is taken from the webpage of the Oslo Zoo Senter.

The running wheel was in a separate cage attached to the rat´s home cage by a tube. The rat had free access to the running wheel at all times. The running distance of every rat was measured by a bike computer. This computer was attached to the top of the running wheel cage.

16 Campden Instruments operant chambers were used in the study. The rat´s working space in eight of the chambers was 25 x 25 x 30 (height) cm and 25 x 25 x 20 (height) cm in the other eight chambers.

Between the testing sessions, the rats were housed in their home cages placed in a rack with allergy filters and a fan producing a low masking noise. The temperature in the room were the rack was kept was about 22 ° C.

Either one or both of retractable levers were used during the training session. A 2.8- W cue light was located above each lever. The rat´s response consisted of pressing on of the levers with deadweight of at least 3 g to activate a micro- switch. The reinforcers consisted of 0.01 ml tap water, and were delivered by a liquid dipper located in a small cubicle. A 2.8- W cue light lid up when a reinforcer was presented. A 7 x 5 transparent plastic lid separated the cubicle from the rat`s working place. The rat could easily open the lid with a light push with the nose or a paw.

Each operant chamber was ventilated and placed in a sound- resistant outer housing. A computer and an online system (SPIDER, Paul Fray, Ltd., UK) recorded the behavior and scheduled the reinforcers (drops of water).

9.3 Response acquisition

The operant conditioning followed the procedure earlier described by Sagvolden and Xu (2008). The first day started with a 30-min habituation session. During this session the lid between the working space and the reinforcement cubicle was open. The house light was on. No lever was present, no cue light above any lever was lid and no water was delivered. After this habituation session, the animals were deprived of water 22 hours a day. The animals had free access to water for an hour after the testing.

On the second day the rats were magazine trained, they had to learn were the water was located. The animals were deprived of water since the day before. The cue lights were not lid and no lever was present. The house light was on. One drop of water was delivered each ten second independent of the rat's behavior. The cue light in the recessed cubicle was lit when water was available. The lid at the opening of the cubicle was kept open all the time. The training sessions took place once in the morning and once in the evening until all rats were trained.

On the third day, the lid at the opening of the recesses cubicle was closed and the rats had to learn how to open the lid to gain access to the water. The house light was on, but the cue lights were not lit and no lever was present.

During the fourth and the fifth day, the rats had to learn to press the left and the right lever respectively to deliver a drop of water. The fourth day, the light over the left lever was lit and the left lever was present. On the fifth day, the light over the right lever was lit and the right lever was present. The house light was on both days.

9.4 Testing

9.4.1 Short program

The short program consisted of six sessions. Both levers were present and the lights above the levers, signaling which one that was correct, shifted randomly. The light was lit above a lever as long as it was the correct lever. Thus, the light was the discriminative stimulus showing the rat which lever it had to press to obtain a drop of water (the reinforcer). Each press of the correct lever resulted in the delivery of the reinforcer. Pressing the wrong lever had no consequences. Each session lasted for 30 minutes. After six sessions with the short program, the rats pressed the correct lever about 80- 85 % of the times.

9.4.2 Long program

The same procedure was repeated in the long program, only the rats were reinforced with water on the average every 180 s. Each session lasted for 90 min. During the session water was delivered 30 times with unpredictable time interval – the shortest less than 1 s and the longest about 12 min. The long program was run for 27 sessions.

9.4.3 Behavioral measures

The total number of presses on the correct and incorrect levers was recorded together with the number of reinforcers delivered. The time between the correct responses (Henton, 1985) were also recorded. The total number of levers presses was used as a measure of degree of *activity*. The percent choice of the correct lever when the reinforcers are delivered infrequently is a measure of *sustained attention*. The number of responses with short IRTs is a measure of degree of *impulsiveness.*

9.5 Statistics

The data were analyzed by repeated measures, MANOVA (Statistica). The significance value was set to .05. The variables used in the analysis were group (SHR male and female) and wheel running (access vs. no access to a running wheel).

10 Results

10.1 General results

The possible effect of the physical exercise is shown in the last six sessions of the long program. All the six tables show the last six sessions, minus session 25. Session 25 was excluded due to a corrupted data file. The three graphs shows all sessions, both from the short and the long program.

The results show no significant effect of exercise. There is a decrease in the performance of both male and female SHR in the long program compared to the short program.

10.2 Attention

Repeated Measures Analysis of Variance (Week ALL DATA AGGREGATED FINAL ATTENTION data repleaced by missing)
Sigma- restricted parameterization
Effective hypothesis decomposition

Effect	SS	Degr. Of Freedom	MS	F	P
Intercept	3101867	1	3101867	1818,323	0,000000
Sex	1363	1	1363	0,799	0,379241
Wheel	4777	1	4777	2,801	0,105783
Sex x wheel	166	1	166	0,097	0,757680
Error	46059	27	1706		

Table 1: Percent correct of the six final sessions, minus session 25 using repeated measures, ANOVA.

Multivariate Test for Repeated Measure: DV_1 (Week ALL DATA AGGREGATED FINAL ATTENTION data repleaced by missing)
Sigma-restricted parameterization
Effective hypothesis decomposition

Effect	Test	Value	F	Effect df	Error df	p
Session	Wilks	0,659635	3,095941	4	24	0,034505
Session x sex	Wilks	0,883829	0,788645	4	24	0,543941
Session x wheel	Wilks	0,963537	0,227059	4	24	0,920545
Session x wheel x sex	Wilks	0,854653	1,020391	4	24	0,416763
Segment	Wilks	0,386533	9,522603	4	24	0,000093
Segment x sex	Wilks	0,838862	1,152545	4	24	0,356202
Segment x wheel	Wilks	0,893586	0,714515	4	24	0,590194
Segment x sex x wheel	Wilks	0,803140	1,470674	4	24	0,242179
Session x segment	Wilks	0,573364	0,558069	16	12	0,863035
Session x segment x wheel	Wilks	0,390406	1,171079	16	12	0,397422
Session x segment x wheel x sex	Wilks	0,571190	0,563049	16	12	0,859435

Table 2: Percent correct of the six final sessions, minus session 25.

Total percent correct lever choice was used as an operationalization of attention. All four groups showed higher percentage of correct responses during the short program compared to the long program. There is no significant effect of wheel running on sustained attention (Tables 1, 2 and Figure 7).

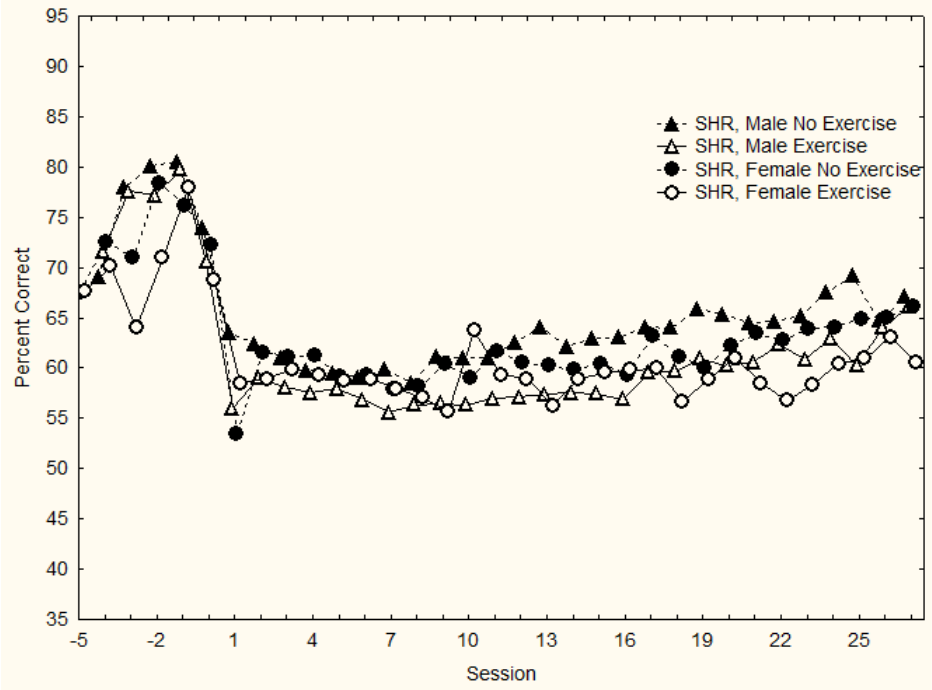


Figure 7: Mean percent correct responses during the short (sessions before session 0) and the long program (from session 0 onwards).

10.3 Activity

Repeated Measures Analysis of Variance (Week ALL DATA AGGREGATED FINAL HYPERACTIVITY data repleaced by missing)
Sigma- restricted parameterization
Effective hypothesis decomposition

Effect	SS	Degr. Of Freedom	MS	F	P
Intercept	81007348	1	81007348	251,5624	0,000000
Sex	572934	1	572934	1,7792	0,19339
Wheel	869172	1	869172	2,6991	0,111999
Sex x wheel	70520	1	70520	0,219	0,643563
Error	8694457	27	322017		

Table 3: Activity measured in the six last sessions, minus session 25.

Multivariate Test for Repeated Measure: DV_1 (Week ALL DATA AGGREGATED FINAL HYPERACTIVITY data repleaced by missing
Sigma-restricted parameterization
Effective hypothesis decomposition

Effect	Test	Value	F	Effect df	Error df	p
Session	Wilks	0,58804	4,20339	4	24	0,010161
Session x sex	Wilks	0,869624	0,89954	4	24	0,479713
Session x wheel	Wilks	0,900725	0,66130	4	24	0,624897
Session x wheel x sex	Wilks	0,838082	1,1592	4	24	0,353372
Segment	Wilks	0,154822	32,75424	4	24	0,000000
Segment x sex	Wilks	0,850602	1,05383	4	24	0,400639
Segment x wheel	Wilks	0,899979	0,66682	4	24	0,621242
Segment x sex x wheel	Wilks	0,904827	0,63110	4	24	0,645092
Session x segment	Wilks	0,349787	1,39416	16	12	0,283543
Session x segment x wheel	Wilks	0,322461	1,57586	16	12	0,215027
Session x segment x wheel x sex	Wilks	0,598741	0,50263	16	12	0,900669

Table 4: Activity measured in the six last sessions, minus session 25.

Activity level was operationalized as the total number of responses. The total number of responses increased from the short to the long program in all four groups. Although males with access to a running wheel tended to be more active, there is no statistically significant effect of wheel running on the total number of responses (Tables 3, 4 and Figure 8).

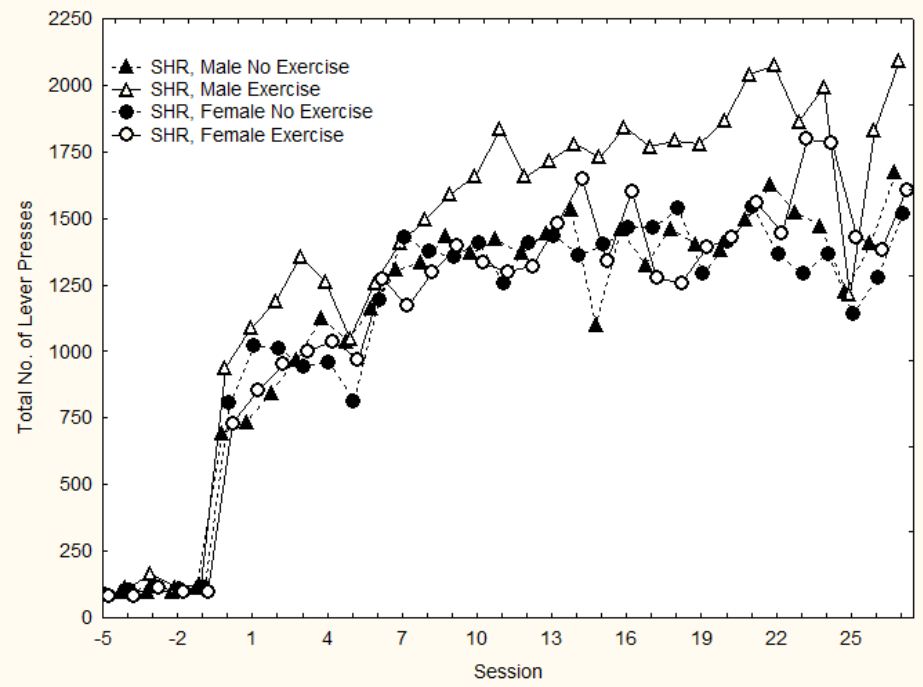


Figure 8: The total number of lever presses during the short (sessions before session 0) and the long program (from session 0 onwards).

10.4 Impulsiveness

Repeated Measures Analysis of Variance (Week ALL DATA AGGREGATED FINAL IMPULSIVENESS LOGTRANSFORMED)
Sigma-restricted parameterization
Effective hypothesis decomposition

Effect	SS	Degr of Freedom	MS	F	P
Intercept	768,6562	1	768,6562	429,1129	0,000000
Sex	0,6635	1	0,6635	0,3704	0,547866
Wheel	0,6272	1	0,6272	0,3501	0,558955
Sex x wheel	2,1947	1	2,1947	1,2252	0,278103
Error	48,3642	27	1,7913		

Table 5: Impulsiveness measured in the last six sessions, minus session 25.

Multivariate tests for repeated measures: DV_1 (Week ALL DATA AGGREGATED FINAL IMPULSIVENESS LOGTRANSFORMED)
Sigma-restricted parameterization
Effective hypothesis decomposition

Effect	Test	Value	F	Effect df	Error df	p
Session	Wilks	0,432702	7,866367	4	24	0,000336
Session x sex	Wilks	0,801254	1,488264	4	24	0,237025
Session x wheel	Wilks	0,952278	0,287476	4	24	0,883194
Session x sex x wheel	Wilks	0,929746	0,453375	4	24	0,768969

Table 6: Impulsiveness measured in the last six sessions, minus session 25.

Impulsiveness was measured as the number of responses with IRTs shorter than 0.67 s. The number of responses with short IRTs increased from the short to the long program in all four groups. There are no statistically significant effect of the wheel running (Tables 5, 6 and Figure 9).

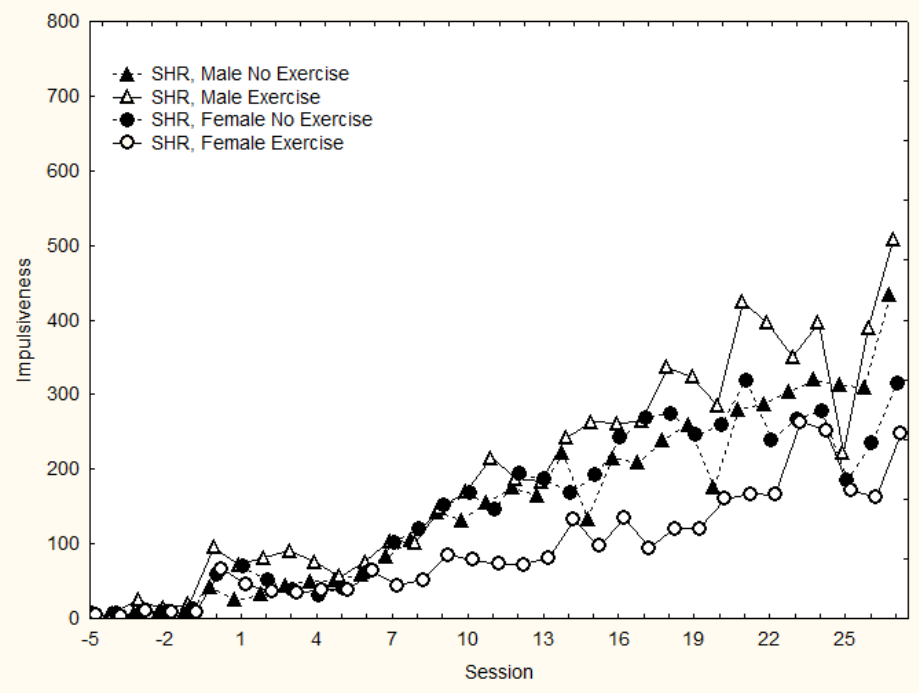


Figure 9: The total number of responses with short IRTs during the short (sessions before session 0) and the long program (from session 0 onwards).

11 Discussion

A common assumption amongst many parents and school teachers appears to be that children with ADHD will benefit from physical exercise (Tantillo et al., 2002). The ADHD child will perform and learn better in e.g. school settings after physical exercise. Scientifically, the support for a direct relationship between physical exercise and better learning and performance in children with ADHD is scarce. In light of the explanations of ADHD behavior given by the arousal theories, we predicted that physical exercise would reduce ADHD-like behavior. The DDT and the Dual-process theory do not suggest beneficial effects of physical exercise. In the light of the everyday assumption of the beneficial effects of physical exercise, the aim of the presenting study was to investigate this possible effect on ADHD-like behavior in an animal model of ADHD. The question was whether physical activity will reduce the behavioral symptoms of ADHD: impaired sustained attention, overactivity and increased impulsiveness. This problem was tested using the SHR/ NCrl substrain, which is a validated model of ADHD (Sagvolden et al., 2009). One male and one female SHR group had free access to a running wheel all the time during the present test program. The other male and female groups did not have such an access.

The results of the presenting study showed no statistically significant effect of exercise on SHR behavior. Neither the male nor the female SHR groups with access to the running wheel improved their sustained attention, reduced their activity level or their impulsiveness as measured in the operant conditioning task.

The arousal theories of ADHD claim that underarousal (Sergeant, 2000) or underactivation (Satterfield and Dawson, 1971; Zentall, 1975) produces impulsive, hyperactive and inattentive behavior. Thus, the arousal theories of ADHD predict that the ADHD child could benefit from physical activity by raising the levels of activation or arousal to a more normal level. The optimal stimulation theory of Zentall (1975) sees activity as a regulator that maintains an optimal stimulation for the underaroused child. Physical activity will, according to the optimal stimulation theory, enhance the arousal level in the child, producing less inattentive, hyperactive and impulsive behavior. The predictions from the arousal theories were not supported by our data.

A relevant question to ask here is how we can determine "optimal" stimulation. According to the Yerkes-Dodson law, the relationship between arousal and performance is shaped as an inverted-U (Sanders, 1983). This means that the individual need a certain level of arousal to perform at an optimal level. Higher level of activation or arousal will lead to decreased performance. Optimal stimulation is therefore difficult to define. Taking this into account, one assumption is that the SHR in this study are too activated or aroused, so the running will have no positive effect on the performance. One way to control this in a better way would be to introduce a resting period for the animals before the testing sessions. The animals in the presenting study, however, had *free* access to the running wheel and were *not forced* to run. This free choice of running will reduce the amount of stress in the animals (Cotman and Berchtold, 2002). It is reasonable to assume that the animals will adjust their running and not get exhausted or overaroused, leaving no basis for the inverted-U as an explanation for the no effects of running. If appealing to an inverted-U as an explanation, one would also expect a decrease in the performance of the exercise group of SHR due to a too high level of arousal. This is not the case in this study. The study didn`t reveal any positive effect of physical exercise, nor a negative effect. The definition of an optimal state is also a problem in the cognitive-energetic model. An optimal state will depend on the context or the task in question. There will also be individual differences in the definition of an optimal state (Johnson et al., 2009). This makes the concept hard to operationalize and measure. McMorris and colleagues (1999) did not revealed any effect of exercise on performance. Their results do not support the idea of an overarousal in explaining the decrease in performance. Instead, they focus on individual cognitive abilities in explaining the differences in performance (McMorris et al., 1999). Winter and colleagues found an immediate effect of physical exercise on learning in a group of healthy male sport student. These results support an effect of exercise close in time before a learning setting (Winter et al., 2007). However, there is a difference in testing healthy individuals without any learning difficulties and individuals suffering from a condition like ADHD. One would assume that the learning conditions for these two groups are initially rather different.

The two other main theories in this paper, the DDT and the dual-process theory, explain ADHD behavior in a different manner than the arousal theories. The role of dopamine is central (Sagvolden et al., 2005; Sonuga-Barke, 2005), and the concepts of reinforcement and extinction is used in trying to explain the cause of the behavior seen in ADHD (Sagvolden et al., 2005). According to the DDT, the motivation behind behavior is reinforcement

(Sagvolden et al., 2005). Reinforcement is the fundament behind learning and the DDT claims that the SHR will continue to press the lever because it associates this behavior with delivery of water. The DDT and the Dual-process theory do not predict any effect of physical exercise on the behavioral symptoms of ADHD.

The arousal theories relate arousal to event rate. The ADHD child will perform better on a task with fast event rate compared to tasks with slow or moderate event rate (Sergeant, 2000). A support for this claim comes from the study by Börger and van der Meere (2000), showing a worse performance of the ADHD children during the slow condition in a go/ no-go task. The SHR in the presenting study were tested on both a short and a long program. During the short program the reinforcers were delivered immediately after the response, producing a fast event rate. In the long program the reinforcers were delivered on the average of every 180 second, producing a slow event rate. If the state of overarousal could explain the missing effect of physical exercise, one would predict a worse performance in the short program compared to the long program. Looking at the results of this study, the performance of the SHR is better during the short program as predicted by the DDT. This is supported in a study by Aase and Sagvolden (2006). They tested one group of children diagnosed with ADHD and one group of children without the diagnosis using different reinforcement intervals. Differences between the groups were found only when the reinforcers were delivered infrequently in time (Aase and Sagvolden, 2006). This give rise to the effect of reinforcers on performance, supporting the DDT as the main theory of ADHD. Another explanation for the decrease in performance in task with slow event rate is the lack of motivation due to a delay aversion in the children with ADHD, as explained in the dual-pathway model (Sonuga-Barke, 2002).

The practical implication to draw from this study is that the ADHD child would not benefit from physical exercise. Having available physical activities for the child in school settings will not improve the learning conditions for that child. Different behavior therapy has been effective in making the ADHD child less active and more attentive in school settings (Barkley, 2002). It seems like different forms of behavior therapy will be more effective for children with ADHD than physical exercise. The presenting study does not support a causal link between physical exercise and reduction in the behavioral symptoms of ADHD. Instead, the theoretical foundation behind the DDT and the dual-pathway model is supported.

One of the arguments for an effect of physical exercise on children diagnosed with ADHD is reports from parents and teachers supporting this effect (Tantillo et al., 2002). It is impossible to consider the scientific value of these parents- and teacher's reports without having access to them. This is a general problem in the literature on the effect of physical exercise on ADHD. Another problem in the research on a possible effect of physical exercise on ADHD behavior is that the few studies available only use one or maybe two children in their testing groups (Tantillo et al., 2002). This makes generalization to the population of children with ADHD almost impossible. Different web pages of ADHD recommend physical exercise, but the empirical support for this is missing. This makes the discussion of whether there is an effect of exercise or not harder and more speculative.

Although the SHR is viewed as a validated animal model of ADHD (Hopkins et al., 2009; Sagvolden, 2000; Sagvolden and Xu, 2008), is important to take into account the possibility of generalizing the results of this study to children with ADHD. The question of generalization is an important consideration in all animal studies with the aim to reflect a disorder or a condition in humans.

Finally, it is important to state that the presenting results say nothing about the health effect of physical exercise in general. Physical exercise has documented effects on both physical (Dishman et al., 2006) and mental health (Hopkins et al., 2009). Different studies also indicate an effect of physical exercise on the dopamine levels in the brain (de Castro and Duncan, 1985; Hattori et al., 1994; Meeusen, 1995; Winter et al., 2007). There is a possibility that the established influence of dopamine in both physical exercise and ADHD could link the two together, but this is not included in this paper.

12 Conclusions

The present study did not reveal any significant effect of wheel running on the SHR behavior, and therefore do not support the arousal theories of ADHD. The interpretation of this is that other mechanisms affects the learning processes, and the results of the study support the role of reinforcement as indicated by the DDT and the dual-pathway model. The four SHR groups performed better and were less hyperactive and impulsive in the short program compared to the long program. Further, there were no differences between the groups with access to the running wheel and the groups without the access. The results support the DDT as the main theory in explaining ADHD. The everyday assumption that children suffering from ADHD will benefit from physical exercise before entering a situation that requires concentration is not supported. In this sense it is important to continue the investigation of alternative treatments of ADHD. Further investigations on the SHR should be looking for possible alterations in dopamine levels after wheel running. This can give us more knowledge about the relationship between dopamine and physical exercise.

13 Reference List

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